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(71) Applicant *(for all designated States except US)*: C-CHEM AG [CH/CH]; Hauptstrasse 67, CH-4102 Binningen (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ELLMERER-MUELLER, Ernst [AT/AT]; Institut für Organische Chemie, Leopold-Franzens-Universität Innsbruck, Innrain 52A, A-6020 Innsbruck (AT). BRÖSSNER, Dagmar [DE/AT]; Conradstrasse 6, A-6020 Innsbruck (AT). MASLOUH, Najib [AT/AT]; Holzhammerstrasse 11, A-6020 Innsbruck (AT). AMBROSI, Horst-Dieter [DE/DE]; Schwarzmeerstrasse 20, D-10319 Berlin (DE). JAS, Gerhard [DE/DE]; Falkenhausenweg 15, D-12249 Berlin (DE).

(74) Agent: KUNZ, Ekkehard; Agrolinz Melamin GmbH, Patentabteilung, St.-Peter-Strasse 25, A-4021 Linz (AT).

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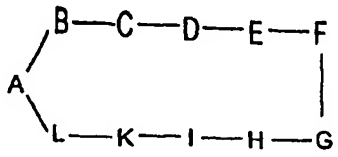

(I)

(57) Abstract

Compounds of formula (I) and their pharmaceutically acceptable salts wherein the letters A to L have the meaning indicated in the description and processes for their preparation and their uses.

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Novel cyclosporins

The present invention relates to novel cyclosporins, processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them. Furthermore, this invention discloses a novel general method for the exchange of substituents at the sarcosine residue of the cyclosporin macrocycle.

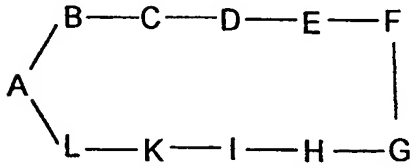
Cyclosporin A is well known for its immunosuppressive and antiinflammatory properties but many biological properties have been described in addition.
EP 0 194 972 describes cyclosporin derivatives with substituents on the sarcosine in position 3 of the macrocycle, the introduction of such substituents, as well as the immunosuppressive, antiinflammatory and antiparasitic activity of these cyclosporin derivatives. EP 0 484 281 describes cyclosporin derivatives with reduced immunosuppressive potency and activity against HIV.
The present invention discloses novel cyclosporins which can be used for the treatment of infectious diseases, of chronic inflammatory and autoimmune diseases, to prevent cardiac hypertrophy, to treat and prevent ischemia and reperfusion injury, to treat neurodegenerative diseases, and to induce processes of tissue regeneration.
A second embodiment of the present invention is a novel method to prepare cyclosporins with substituents at the sarcosine in position 3 of the macrocycle. EP 0 194 972 describes the introduction of certain substituents at the sarcosine. The method described in EP 0 194 972 involves treatment of a cyclosporin with strong base to generate a polyanion and subsequent reaction of this polyanion with electrophiles, such as disulfides, alkyl halides or other suitable alkylating agents. Halogens or sources of positive halogen can also be used, as well as aldehydes. There is no example in the prior art which describes the exchange of such a substituent by another. The present invention discloses such a method. In this novel method, a suitable substituent is first introduced into a cyclosporin polyanion and the resulting product is isolated. The substituent is subsequently activated to become a leaving group and replaced by the desired novel substituent. This novel method

allows the introduction of a wide variety of substituents into the sarcosine residue of the cyclosporin macrocycle.

The cyclosporin nomenclature and numbering systems used hereafter are those used by J. Kallen et al., "Cyclosporins: Recent Developments in Biosynthesis, Pharmacology and Biology, and Clinical Applications", Biotechnology, second edition, H.-J. Rehm and G. Reed, ed., 1997, p535-591 and are shown below:

Position numbering	Letter in Formula I	Amino acid in cyclosporin A
1	A	N-Methyl-butenyl-threonine (MeBmt)
2	B	α-aminobutyric acid (Abu)
3	C	Sarcosine (Sar)
4	D	N-Methyl-leucine (MeLeu)
5	E	Valine (Val)
6	F	N-Methyl-leucine (MeLeu)
7	G	Alanine (Ala)
8	H	(D)-Alanine ((D)-Ala)
9	I	N-Methyl-leucine (MeLeu)
10	K	N-Methyl-leucine (MeLeu)
11	L	N-Methylvaline (MeVal)

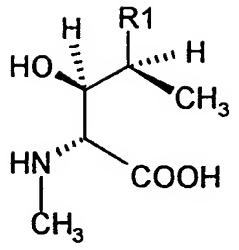
Objects of the present invention are therefore compounds of the formula I



Formula I

and their pharmaceutically acceptable salts wherein the letters A to L represent residues of the following amino acids:

A (L)-alpha-N-methylamino-beta-hydroxy acid of the formula II,

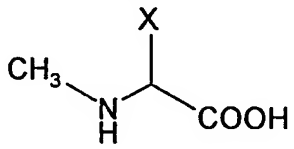


Formula II

wherein R1 is n-butyl or butenyl-1,

B alpha-amino-butyric acid, alpha-amino-valerianic acid (norvaline), threonine, or valine,

C substituted sarcosine of the formula III



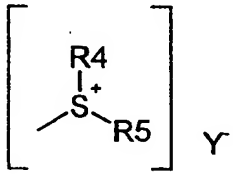
Formula III

in which X is

$S-(O)_n-R2$, in which n has the value zero, one or two and R2 is hydrogen, unsubstituted or substituted, unbranched or branched, acyclic, monocyclic or polycyclic, satutared or unsaturated lower alkyl, substituted or unsubstituted aryl or heteroaryl, or

X is O-R3, in which R3 is hydrogen, unsubstituted or substituted, unbranched or branched, saturated or unsaturated, acyclic, monocyclic or polycyclic lower alkyl, or acyl, or

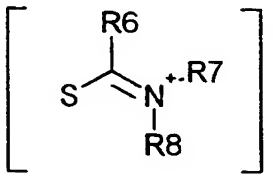
X is sulfonium groups of the formula IV,



Formula IV

in which R4 and R5 are independently selected from lower alkyl, aryl, or heteroaryl and Y^- is an anion, or

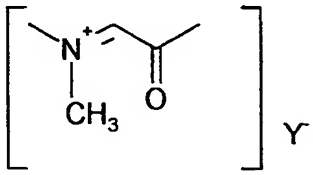
X is a group of the formula V,



Y⁻ Formula V

in which R6 and R7 are independently selected from lower alkyl or aryl or form together a ring and R8 is hydrogen or substituted or unsubstituted lower alkyl and Y⁻ is an anion, or

C is a residue of the formula VI and Y⁻ is an anion,



Y⁻ Formula VI

D N-methyl-leucine, gamma-hydroxy-N-methyl-leucine, N-methyl-valine, or N-methyl-isoleucine,

E valine,

F N-methyl-leucine,

G alanine,

H glycine, (D)-alanine, (D)-serine, O-hydroxyethyl-(D)-serine,

I,K N-methyl-leucine, and

L N-methyl-valine.

The 1-butenyl rest in A has preferrably the trans configuration.

Examples for lower alkyl are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, isopentyl, tert-pentyl, neopentyl, hexyl and its isomers.

Examples for monocyclic lower alkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Examples for polycyclic lower alkyl groups are bicylo[2.1.1]hexyl, norbornyl, bicyclo[2.2.2]octyl.

Examples for unsaturated lower alkyl are vinyl, allyl, butenyl, pentenyl, pentadienyl, hexenyl, hexadienyl.

Examples for substituents in these radicals are hydroxy, methoxy, ethoxy, propoxy, isopropoxy, amino, monoalkylamino, dialkylamino, acylamino, halogen, acyl, carboxy, carbamido.

Examples for monoalkylamino are methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, 1-pentylamino, 2-pentylamino, 3-pentylamino, isopentylamino, tert-pentylamino, neopentylamino, hexylamino and its isomers.

Examples for dialkylamino are N,N-dimethylamino, N-methyl-N-ethylamino, N,N-diethylamino, N-propyl-N-methylamino, N-methyl-N-isopropylamino, dipropylamino, diisopropylamino, N-butyl-N-methylamino and its isomers, N-butyl-N-ethylamino and its isomers, N-butyl-N-propylamino and its isomers, N,N-dibutylamino and its isomers.

The alkyl groups of dialkylamino may also form a ring together. Examples are azetidine, pyrrolidine, piperidine, morpholine, piperazine, N'-alkylpiperazine, azabicylo[2.1.1]hexane, azanorbornane, azabicyclo[2.2.2]octane.

Examples for acyl are formyl, acetyl, propionyl, butyryl, pivaloyl, benzoyl, alkoxycarbonyl.

Examples for acylamino are N-formylamino, N-acetylamino, N-tert-butoxycarbonyl-amino, N-benzyloxycarbonyl-amino, N-benzoyl-amino, N-phthaloyl.

Examples for substituted aryl are tolyl, chlorphenyl, methoxyphenyl, aminophenyl, dimethylaminophenyl, 1-naphthyl, 2-naphthyl.

Examples for heteroaryl are thiazole, oxazole, imidazole, pyridine, pyrazole, pyrimidine, pyrazine, triazine, benzthiazole, benzoxazole, benzimidazole.

Examples of sulfonium groups are dimethylsulfonium, S-methyl-S-phenylsulfonium, S-methyl-S-allylsulfonium, S-methyl-S-carboxamidomethyl-sulfonium, S-dodecyl-S-methylsulfonium.

Examples for groups of the formula V are N-methyl-pyridinium-2-ylthio, N-methyl-pyridinium-4-ylthio, N-methyl-triazinylthio, N-methyl-benzthiazol-2-ylthio, pyridinium-2-ylthio toluenesulfonate, pyridinium-4-ylthio toluenesulfonate, pyridinium-2-ylthio methanesulfonate.

Compounds of the formula I in which C is a sarcosine substituted by S-R2 are prepared by forming polyanions from cyclosporins in which C is sarcosine and

reacting these polyanions with appropriate sulfur electrophiles like disulfides, thiolsulfinates, sulfenyl halides, or disulfide-derived sulfonium salts. The polyanions are in turn prepared by treating the cyclosporins in an appropriate solvent at low temperature with an excess of a strong base. Examples for strong bases are alkali amides like lithium amide, natrium amide, lithium diisopropylamide or lithium hexamethyl disilazide. Examples for inert solvents used for these reactions are tetrahydrofurane, dioxane, diethylether, methyl tert-butylether, or liquid ammonia.

Compounds of the formula I in which C is sarcosine substituted by S-R2 are furthermore prepared by exchanging the substituent X in compounds of formula I in which C is sarcosine substituted by X and where X is a residue of formula IV or formula V by thiols HS-R2, in which R2 is lower alkyl, aryl, or acyl.

A compound of the formula I in which C is sarcosine substituted by S-R2 in which R2 is hydrogen is prepared by treating compounds of formula I in which C is sarcosine substituted by S-R2 and in which R2 is acyl in an appropriate solvent with ammonia, hydrazine, hydroxylamine, or organic derivatives thereof, such as methylamine, benzylamine, methylhydrazine, or dimethylhydrazine. Appropriate solvents for these reactions are alcohols, such as methanol or ethanol, ethers such as diethylether, tetrahydrofurane, or dioxane, or inert aprotic solvents, such as dimethyl formamide. The resulting thiol can be isolated but is more conveniently alkylated directly by adding to these reactions an alkylating agent such as an alkyl halide or esters of alcohols with sulfuric acid, or organic sulfonic acids such as 4-toluene sulfonic acid, methane sulfonic acid, or trifluoromethane sulfonic acid. The present invention makes it therefore possible to produce compounds of the formula I in which C is sarcosine substituted by S-R2 in which R2 is substituted or unsubstituted, branched or unbranched, saturated or unsaturated, acyclic, monocyclic, or polycyclic lower alkyl.

Compounds of the formula I in which C is a sarcosine substituted by SO-R2 and by SO2-R2 are prepared by treating compounds of formula I in which C is sarcosine substituted by S-R2 with an appropriate oxidant in an inert solvent. Examples for such oxidants are hydrogen peroxide, sodium chlorate, sodium periodate, peroxyacetic acid, meta-chloroperbenzoic acid, or potassium persulfate. Solvents for these reactions are for example mixtures of water with organic solvents such as

tetrahydrofurane, dioxane or acetic acid, or anhydrous organic solvents such as dichloromethane, chloroform, tetrachloroethane, tetrahydrofurane, or dioxane.

Compounds of the formula I in which C is a sarcosine substituted by O-R3 can be prepared by exchanging the substituent S-R2 in compounds of formula I in which C is sarcosine substituted by S-R2. This exchange reaction is effected by metal salts which have an affinity for sulfur, such as mercuric acetate, silver acetate, copper acetate and others, but can also be effected by the presence of Bronsted or Lewis acids. The acidic nature of Bronsted acids is due to their capacity to act as proton donors. Such acids are for example sulfuric acid, toluene sulfonic or camphersulfonic acid, hydrochloric acid, but also acetic acid, formic acid and other organic carboxylic acids. Lewis acids are compounds having affinity for free electron pairs and forming coordination complexes with groups having free electron pairs. Examples for Lewis acids are boron trifluoride, titanium tetrachloride, aluminum chloride, or zinc chloride. Such Bronsted or Lewis acids or metal salts convert S-R2 or O-R3 substituents at the sarcosine position of the cyclosporin macrocycle into leaving groups, forming an intermediary cation of the formula VI which can then further react with nucleophiles present in the reaction mixture to form the desired products.

The present invention makes it therefore also possible to exchange one given O-R3 substituent for another O-R3' substituent by using the reaction conditions as described above.

A compound of formula I in which the amino acid residue of C is the cation of Formula VII is a common intermediate for these exchange reactions. This type of cation is well known to experts in the field and is analogous to the commonly accepted intermediate in the Mannich reaction. In the case of cyclosporins, however, such an intermediate has never been described and is new. Mannich reactions are used to introduce aminoalkyl residues into a wide variety of nucleophiles, such as enols, phenols, enamines, heterocycles such as indole, pyrrol, or furane. Other nucleophiles reacting with such cations are allyl and vinylsilanes and –stannanes as well as acetylenes. Therefore, cyclosporins in which the amino acid residue of C is the cation of Formula VII are an especially preferred embodiment of the present invention.

The compounds of the present invention act on enzymes called cyclophilins and inhibit their catalytic activity. Cyclophilins occur in a wide variety of different organisms, including human, yeast, bacteria, protozoa, metazoa, insects, plants, or viruses. In the case of infectious organisms, inhibition of the cyclophilin catalytic activity by compounds of the present invention often results in an inhibitory effect on the organism. Furthermore, in humans the catalytic activity of cyclophilins plays a role in many different disease situations. Inhibition of this catalytic activity is often associated to a therapeutic effect. Therefore, the compounds of the present invention can be used for the treatment of infections including that by HIV as well as fungal pathogens, protozoan and metazoan parasites. Furthermore, the compounds of the present invention can be used to treat chronic inflammatory and autoimmune diseases including but not limited to rheumatoid arthritis, psoriasis, and uveitis. In addition, the compounds of the present invention can be used to treat neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and neuropathies.

Another use of the compounds of the present invention is protection against tissue damage associated to ischemia and reperfusion such as paralytic damage after spinal cord or head injuries or cardiac damage after myocardial infarct.

Furthermore, the compounds of the present invention induce regenerative processes such as that of hair, liver, gingiva, or nerve tissue damaged or lost due to injury or other underlying pathologies, such as damage of the optical nerve in glaucoma.

The compounds of the present invention can, together with pharmaceutically acceptable additives and/or excipients be administered either orally in the form of capsules, tablets, or drink solutions or parenterally in form of acute injections or infusions. They can also be applied locally in form of solutions, eye drops, or as gels and ointments. For topical and parenteral applications it is of special advantage that, unlike cyclosporin A, many of the compounds of the present invention have basic substituents which enable the formation of salts with physiologically acceptable acids.

The daily administered dosage depends on the structure of the medicament, the disease to be treated, and the type of formulation and is from about 1 mg to about 200 mg per kg body weight.

Examples

1. 3-(Pyridyl-4-thio)-cyclosporin:

Liquid ammonia (200 ml) is condensed in a flask under argon. Freshly cut sodium (1.78 g, 75 mmol) is added in 4 portions, followed by one crystal of ferric nitrate. The mixture is vigorously stirred for 15 minutes, at which time a dark grey color persists. A solution of cyclosporin A (5 g, 4 mmol) in tert.-butylmethyl ether (90 ml) is added over 15 minutes and the mixture is stirred at minus 40° Celsius for 1.5 hrs. Then, a solution of 2,2'-dipyridyl disulfide (7.2 g, 33 mmol) in 70 ml tert.-butylmethyl ether is added and stirring continued for 2 hrs at minus 35° -minus 40°. Solid ammonium chloride (5.56 g, 104 mmol) is added, stirring continued at minus 35° for 10 minutes. After warming to room temperature, the mixture is stirred for another 2 hrs, filtered, the residue washed 3 times with tert.-butylmethyl ether, and filtrate and washings combined, extracted with 2N sodium hydroxide, brine and dried over sodium sulfate. Chromatography of the residue obtained upon evaporation on silica, eluting with diethyl ether/methanol = 96/4 yielded the title compound as two isomers.

The ^{1}H-NMR chemical shift of the proton at the sarcosine residue [δ(H3)] for isomer A of the title compound is at 6.36 ppm, for isomer B at 7.13 ppm. The corresponding values in the ^{13}C-NMR [δ(C3)] are 58.81 and 58.45 ppm.

Analogous to example 1 the following disulfides were used to prepare the following products:

Example	Disulfide	Product
2	2,2'-dipyridyldisulfid	3-(Pyridyl-4-thio)-cyclosporin A
3	2,2'-dipyridyldisulfid	3-(Pyridyl-2-thio)-4-(γ-hydroxy-methylleucine)-cyclosporin
4	2,2'-dipyridyldisulfid	3-(Pyridyl-2-thio)-4-methylvaline-cyclosporin

5	2,2'-dipyridyldisulfid	3-(Pyridyl-2-thio)-2-norvaline-cyclosporin
6	2,2'-dipyridyldisulfid	3-(Pyridyl-2-thio)-2-valine-cyclosporin
7	2,2'-dipyridyldisulfid	3-(Pyridyl-2-thio)-8-(D)-serine-cyclosporin
8	diphenyldisulfid	3-(Phenylthio)-cyclosporin A
9	2,2'-dimethylaminoethyldisulfid	3-(2-dimethylaminoethylthio)-cyclosporin
10	2,2'-mercaptobenzthiazolyl-disulfide	3-(Mercaptobenzthiazol-2-ylthio)-cyclosporin

The products of these examples have the following physiochemical data:

Example	Product	δ (H3) (CDCl3)	δ (C3) (CDCl3)	Calc Mass	High Resolution MS
2	3-(Pyridyl-4-thio)-cyclosporin A				
	isomer A	6.36	60.19	1311.84	1311.8850
	isomer B	7.13	58.46		
3	3-(Pyridyl-2-thio)-4-(γ-hydroxy-methylleucine)-cyclosporin	7.12	58.58	1327.84	1327.7922
4	3-(Pyridyl-2-thio)-4-methylvaline-cyclosporin	7.12	58.45	1297.83	1297.7507
5	3-(Pyridyl-2-thio)-2-norvaline-cyclosporin	7.12	58.77	1325.86	1325.8316
6	3-(Pyridyl-2-thio)-2-valine-cyclosporin				
	isomer A	7.08	58.81	1325.86	1325.8517
	isomer B	7.33	58.45		

7	3-(Pyridyl-2-thio)-8-(D)-serine-cyclosporin	7.11	58.12		
	Isomer A	7.60	57.63	1327.84	1327.8436
	Isomer B				
8	3-(Phenylthio)-cyclosporin A	6.18	63.62	1310.85	1310.8732
9	3-(2-dimethylaminoethylthio)-cyclosporin	5.77	59.32	1305.89	1305.8762
10	3-(Mercptobenzthiazol-2-ylthio)-cyclosporin,				
	Isomer A	7.0	63.00	1367.86	1366.8120
	Isomer B	7.56	60.90		

11. 3'-Acetoxy-3-phenylthio-cyclosporin

To a stirred solution of 700 mg the product of example 8 and 300 mg of 4-dimethylamino pyridine in 3 ml pyridine was added 0.5 ml acetic anhydride. The solution was stirred at ambient temperature for 36 hrs and then diluted with 20 ml cold water. The mixture was extracted three times with ethyl acetate, the organic extracts were combined and washed successively with 1N sulfuric acid, water, brine and dried over sodium sulfate. The residue obtained from evaporation to dryness was chromatographed on silicagel using ethyl acetate as eluent. The title product was obtained as yellow foam.

12. 3',3-Diacetoxy-cyclosporin

The product of example 11 (100 mg) was dissolved in 2 ml acetic acid, mercuric acetate (100 mg) was added and the mixture was heated to 50° for 3 hrs. After evaporation to dryness the residue was taken up in ethyl acetate and washed with sodium bicarbonate solution. The organic phase was dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on silica gel yielded 45 mg of the title compound. The characteristic

NMR signals of this compound in deuterochloroform are at 6.80 ppm (sarcosine H) and 74.53 ppm (sarcosine C).

13. 3-Acetoxy-cyclosporin: To a stirred solution of 500 mg of the product of example 8 in 3 ml acetic acid was added silver acetate (100 mg) and the mixture was warmed to 50o for 20 hrs. After evaporation to dryness the residue was taken up in ethyl acetate and washed with sodium bicarbonate solution. The organic phase was dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on silica gel yielded 45 mg of the title compound. The characteristic NMR signals of this compound in deuterochloroform are at 6.82 ppm (sarcosine H) and 74.40 ppm (sarcosine C).

14. 3-Methoxycyclosporin

The product of example 1 (131 mg) was dissolved in 2 ml methanol, camphersulfonic acid (25 mg) was added and the mixture heated to 50° for 5 hrs. After addition of aqueous ammonia (0.5 ml) and evaporation to dryness the residue was taken up in ethyl acetate and washed with sodium bicarbonate solution. The organic phase was dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on silica gel yielded 45 mg of the title compound. The characteristic NMR signals of this compound in deuterochloroform are at 5.84 ppm (sarcosine H) and 83.30 ppm (sarcosine C).

This compound is also prepared under identical conditions using the product of example 12 as starting material in place of the product of example 1.

Analogous to example 14 the following alcohols were used to prepare the following products:

Example	Alcohol	Product	δ(H3) (CDCl3)	δ(C3) (CDCl3)
15	Ethanol	3-Ethoxycyclosporin	5.93	81.58
16	Isopropyl alcohol	3-Isopropyloxycyclosporin	6.02	79.50

17. [D-Sar-(tert.-butoxy)^3]-cyclosporin: Following the procedure of example 14 but using the product of example 10 instead of the product of example 1 and using tert.-butanol instead of methanol, the title compound is obtained. The characteristic NMR signals of this compound in deuterochloroform are at 6.09 ppm (sarcosine H) and 76.00 ppm (sarcosine C). The calculated mass is 1274.74, the mass determined by high resolution MS is 1273.898884.

18. [D-Sar-(allyloxy)^3]-cyclosporin: Following the procedure of example 17 and using allyl alcohol in place of tert.-butanol, the title compound is obtained. The characteristic NMR signals of this compound in deuterochloroform are at 5.96 ppm (sarcosine H) and 80.80 ppm (sarcosine C). The calculated mass is 1258.69, the mass determined by high resolution MS is 1257.867583.

19. [D-Sar-(hydroxy)^3]-cyclosporin: The product of example 1 (130 mg) was dissolved in 2 ml tetrahydrofurane, 1N sulfuric acid (1 ml) was added and the mixture heated to 50° for 5 hrs. After addition of aqueous ammonia (0.5 ml), ethyl acetate was added, the mixture was vigorously shaken and, after separation of the organic layer it was washed with sodium bicarbonate solution. The organic phase was dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on silica gel yielded 55 mg of the title compound. The characteristic NMR signal of this compound in

deuterochloroform is at 6.96 ppm (sarcosine H). The calculated mass is 1218.63, the mass determined by high resolution MS is 1217.836248.

20. [D-Sar-(acetylthio)^3]-cyclosporin: The product of example 1 (500 mg) was dissolved in 2 ml tetrahydrofurane and 2 ml thioacetic acid. Camphersulfonic acid (200 mg) was added and the mixture heated to 50° for 5 hrs. After addition of aqueous ammonia (1 ml), ethyl acetate was added, the mixture was vigorously shaken and, after separation of the organic layer it was washed with sodium bicarbonate solution. The organic phase was dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on silica gel yielded 255 mg of the title compound. The characteristic NMR signals of this compound in deuterochloroform are at 6.50 ppm (sarcosine H) and 57.60 ppm (sarcosine C). The calculated mass is 1276.73, the mass determined by high resolution MS is 1276.824005.

21. [D-Sar-(methylthio)^3]-cyclosporin: Under argon atmosphere, the product of example 19 (120 mg) was dissolved in 1 ml ethanol. N,N-dimethylhydrazine (60 mg) was added and the mixture stirred at room temperature for 5 hrs. After addition of methyl iodide (0.5 ml) stirring was continued over night. The mixture was concentrated to dryness and the residue partitioned between ethyl acetate and 1N sulfuric acid. The organic layer was washed with sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate and evaporated to dryness. Chromatography of the residue on silica gel yielded 75 mg of the title compound. The compound has the following optical rotation: $[\alpha]^{20}_D$ = –215° , c = 1, CHCl3. A value of $[\alpha]^{20}_D$ = –215° , c = 1, CHCl3, has been reported for this compound.

22. [D-Sar-(2-(N-Boc-3-aminopropoxy))^3]-cyclosporin: The product of example 10 (140 mg) was dissolved in 5 ml dry tetrahydrofurane, 175 mg N-Boc-3-aminopropanol and Camphersulfonic acid (30 mg) were added and the mixture heated to 50° for 12 hrs. The mixture was evaporated to dryness, the residue taken up in ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, the organic phase was dried over sodium sulfate and evaporated to dryness. Repeated chromatography of the residue on silica

gel yielded 75 mg of the title compound and 23 mg [D-Sar-(2-(3-aminopropoxy))^3]-cyclosporin. The characteristic NMR signal of the title compound in deuterochloroform is at 5.97 ppm (sarcosine H), that of [D-Sar-(2-(3-aminopropoxy))^3]-cyclosporin at 5.91 ppm.

According to the procedure described in example 22 and using the following alcohols the following products are obtained:

Example	Alcohol	Product
23	N-Boc-2-aminoethanol	[D-Sar-(2-(N-Boc-3-aminoethoxy))^3]-cyclosporin
24		[D-Sar-(2-(3-aminoethoxy))^3]-cyclosporin
25	N-Boc-5-aminopentanol	[D-Sar-(2-(N-Boc-3-aminopentoxy))^3]-cyclosporin
26		[D-Sar-(2-(3-aminopentoxy))^3]-cyclosporin
27	N,N-dimethyl-aminoethanol	[D-Sar-(2-(N,N-dimethylaminoethoxy))^3]-cyclosporin
28	N,N-diethylaminoethanol	[D-Sar-(2-(N,N-diethylaminoethoxy))^3]-cyclosporin
29	N-methyl-N-(1,1-dimethyl-ethyl)-aminoethanol	[D-Sar-(2-(N-methyl-N-(1,1-dimethyl-ethyl)-2-aminoethoxy))^3]-cyclosporin
30	N-phthaloyl-aminoethanol	[D-Sar-(2-(N-phthalimido-2-aminoethoxy))^3]-cyclosporin
31	N-Boc-2-amino-3-phenylpropanol	[D-Sar-(2-(N-Boc-2-amino-3-phenyl-propoxy))^3]-cyclosporin
32	N-Boc-2-hydroxymethyl-pyrolidine	[D-Sar-(2-(N-Boc-pyrrolidine-2-yl)-methoxy)^3]-cyclosporin
33		[D-Sar-(2-(pyrrolidine-2-yl)-methoxy)^3]-cyclosporin
34	N-methyl-4-hydroxypiperidine	[D-Sar-(2-(N-methyl-piperidine-4-yl)-oxy)^3]-cyclosporin
35	N-methyl-3-hydroxyazetidine	[D-Sar-(2-(N-methyl-azetidine-3-yl)-oxy)^3]-cyclosporin

The characteristic NMR signals of these compounds are as follows:

Example	Product	δ(H3) (CDCl3)	δ (C3) (CDCl3)
23	[D-Sar-(2-(N-Boc-3-aminoethoxy))^3]-cyclosporin	5.96	82.01
24	[D-Sar-(2-(3-aminoethoxy))^3]-cyclosporin	5.92	81.53
25	[D-Sar-(2-(N-Boc-3-aminopentoxy))^3]-cyclosporin	5.95	81.76
26	[D-Sar-(2-(3-aminopentoxy))^3]-cyclosporin	5.94	81.73
27	[D-Sar-(2-(N,N-dimethylaminoethoxy))^3]-cyclosporin	5.89	80.63
28	[D-Sar-(2-(N,N-diethylaminoethoxy))^3]-cyclosporin	5.88	80.54
29	[D-Sar-(2-(N-methyl-N-(1,1-dimethyl-ethyl)-2-aminoethoxy))^3]-cyclosporin	5.84	80.13
30	[D-Sar-(2-(N-phthalimido-2-aminoethoxy))^3]-cyclosporin	5.99	82.12
31	[D-Sar-(2-(N-Boc-2-amino-3-phenyl-propoxy))^3]-cyclosporin	5.96	81.89
32	[D-Sar-(2-(N-Boc-pyrrolidine-2-yl)-methoxy)^3]-cyclosporin	5.87	79.46
33	[D-Sar-(2-(pyrrolidine-2-yl)-methoxy)^3]-cyclosporin	5.85	79.32
34	[D-Sar-(2-(N-methyl-piperidine-4-yl)-oxy)^3]-cyclosporin	5.85	79.32
35	[D-Sar-(2-(N-methyl-azetidine-3-yl)-oxy)^3]-cyclosporin	6.03	78.50

Using the conditions of example 1 the following compounds can be obtained:

3-(2-Hydroxyethyl)thio-cyclosporin

3-(3-Hydroxypropyl)thio-cyclosporin

3-(2-Aminoethyl)thio-cyclosporin

3-(2-Methylaminoethyl)thio-cyclosporin

3-(2-Ethylaminoethyl)thio-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-cyclosporin

3-(2-Diethylaminoethyl)thio-cyclosporin

3-(2-n-Propylaminoethyl)thio-cyclosporin

3-(2-Isopropylaminoethyl)thio-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-cyclosporin

3-(2-Diisopropylaminoethyl)thio-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-cyclosporin

3-(2-n-Butylaminoethyl)thio-cyclosporin

3-(2-sec-Butylaminoethyl)thio-cyclosporin

3-(2-Isobutylaminoethyl)thio-cyclosporin

3-(2-tert-Butylaminoethyl)thio-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-cyclosporin

3-(2-Azetidinoethyl)thio-cyclosporin

3-(2-pyrrolidinoethyl)thio-cyclosporin

3-(2-piperidinoethyl)thio-cyclosporin

3-(2-morpholinoethyl)thio-cyclosporin

3-(2-piperazinoethyl)thio-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-cyclosporin

3-(3-azetidinyl)thio-cyclosporin

3-(N-methyl-3-azetidinyl)thio-cyclosporin

3-(N-methyl-3-azetidinyl)thio-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–cyclosporin

3-(3-pyrrolidinyl)thio-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–cyclosporin

3-(4-piperidinyl)thio–cyclosporin

3-(N-methyl-4-piperidinyl)thio–cyclosporin

3-(N-methyl-4-piperidinyl)thio–cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–cyclosporin

3-(2-Hydroxyethyl)thio-2-valine-cyclosporin

3-(3-Hydroxypropyl)thio-2-valine-cyclosporin

3-(2-Aminoethyl)thio-2-valine-cyclosporin

3-(2-Methylaminoethyl)thio-2-valine-cyclosporin

3-(2-Ethylaminoethyl)thio-2-valine-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-2-valine-cyclosporin

3-(2-Diethylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Propylaminoethyl)thio-2-valine-cyclosporin

3-(2-Isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-2-valine-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-Diisopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Butylaminoethyl)thio-2-valine-cyclosporin

3-(2-sec-Butylaminoethyl)thio-2-valine-cyclosporin

3-(2-Isobutylaminoethyl)thio-2-valine-cyclosporin

3-(2-tert-Butylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-2-valine-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-2-valine-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-2-valine-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-2-valine-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-2-valine-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-2-valine-cyclosporin

3-(2-Azetidinoethyl)thio-2-valine-cyclosporin

3-(2-pyrrolidinoethyl)thio-2-valine-cyclosporin

3-(2-piperidinoethyl)thio-2-valine-cyclosporin

3-(2-morpholinoethyl)thio-2-valine-cyclosporin

3-(2-piperazinoethyl)thio-2-valine-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-2-valine-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-2-valine-cyclosporin

3-(3-azetidinyl)thio-2-valine-cyclosporin

3-(N-methyl-3-azetidinyl)thio-2-valine-cyclosporin

3-(N-methyl-3-azetidinyl)thio-2-valine-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–2-valine-cyclosporin

3-(3-pyrrolidinyl)thio-2-valine-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–2-valine-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–2-valine-cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–2-valine-cyclosporin

3-(4-piperidinyl)thio–2-valine-cyclosporin

3-(N-methyl-4-piperidinyl)thio–2-valine-cyclosporin

3-(N-methyl-4-piperidinyl)thio–2-valine-cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–2-valine-cyclosporin

3-(2-Hydroxyethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Hydroxypropyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Aminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Methylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Ethylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Diethylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Diisopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Isobutylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Azetidinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-pyrrolidinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-piperidinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-morpholinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-piperazinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-azetidinyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-3-azetidinyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-3-azetidinyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-pyrrolidinyl)thio-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(4-piperidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-4-piperidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-4-piperidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Hydroxyethyl)thio-2-norvaline-cyclosporin

3-(3-Hydroxypropyl)thio-2-norvaline-cyclosporin

3-(2-Aminoethyl)thio-2-norvaline-cyclosporin

3-(2-Methylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Ethylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Diethylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Propylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Diisopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Butylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-sec-Butylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Isobutylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-tert-Butylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-2-norvaline-cyclosporin

3-(2-Azetidinoethyl)thio-2-norvaline-cyclosporin

3-(2-pyrrolidinoethyl)thio-2-norvaline-cyclosporin

3-(2-piperidinoethyl)thio-2-norvaline-cyclosporin

3-(2-morpholinoethyl)thio-2-norvaline-cyclosporin

3-(2-piperazinoethyl)thio-2-norvaline-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-2-norvaline-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-2-norvaline-cyclosporin

3-(3-azetidinyl)thio-2-norvaline-cyclosporin

3-(N-methyl-3-azetidinyl)thio-2-norvaline-cyclosporin

3-(N-methyl-3-azetidinyl)thio-2-norvaline-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–2-norvaline-cyclosporin

3-(3-pyrrolidinyl)thio-2-norvaline-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–2-norvaline-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–2-norvaline-cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–2-norvaline-cyclosporin

3-(4-piperidinyl)thio–2-norvaline-cyclosporin

3-(N-methyl-4-piperidinyl)thio–2-norvaline-cyclosporin

3-(N-methyl-4-piperidinyl)thio–2-norvaline-cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–2-norvaline-cyclosporin

3-(2-Hydroxyethyl)thio-4-methylvaline-cyclosporin

3-(3-Hydroxypropyl)thio-4-methylvaline-cyclosporin

3-(2-Aminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Methylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Ethylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Diethylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Propylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Diisopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Butylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-sec-Butylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Isobutylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-tert-Butylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-4-methylvaline-cyclosporin

3-(2-Azetidinoethyl)thio-4-methylvaline-cyclosporin

3-(2-pyrrolidinoethyl)thio-4-methylvaline-cyclosporin

3-(2-piperidinoethyl)thio-4-methylvaline-cyclosporin

3-(2-morpholinoethyl)thio-4-methylvaline-cyclosporin

3-(2-piperazinoethyl)thio-4-methylvaline-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-4-methylvaline-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-4-methylvaline-cyclosporin

3-(3-azetidinyl)thio-4-methylvaline-cyclosporin

3-(N-methyl-3-azetidinyl)thio-4-methylvaline-cyclosporin

3-(N-methyl-3-azetidinyl)thio-4-methylvaline-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–4-methylvaline-cyclosporin

3-(3-pyrrolidinyl)thio-4-methylvaline-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–4-methylvaline-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–4-methylvaline-cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–4-methylvaline-cyclosporin

3-(4-piperidinyl)thio–4-methylvaline-cyclosporin

3-(N-methyl-4-piperidinyl)thio–4-methylvaline-cyclosporin

3-(N-methyl-4-piperidinyl)thio–4-methylvaline-cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–4-methylvaline-cyclosporin

3-(2-Hydroxyethyl)thio-4-methylisoleucine-cyclosporin

3-(3-Hydroxypropyl)thio-4-methylisoleucine-cyclosporin

3-(2-Aminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Methylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Ethylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Diethylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Propylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Diisopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Butylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-sec-Butylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Isobutylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-tert-Butylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-Azetidinoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-pyrrolidinoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-piperidinoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-morpholinoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-piperazinoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-4-methylisoleucine-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-4-methylisoleucine-cyclosporin

3-(3-azetidinyl)thio-4-methylisoleucine-cyclosporin

3-(N-methyl-3-azetidinyl)thio-4-methylisoleucine-cyclosporin

3-(N-methyl-3-azetidinyl)thio-4-methylisoleucine-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–4-methylisoleucine-cyclosporin

3-(3-pyrrolidinyl)thio-4-methylisoleucine-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–4-methylisoleucine-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–4-methylisoleucine-cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–4-methylisoleucine-cyclosporin

3-(4-piperidinyl)thio–4-methylisoleucine-cyclosporin

3-(N-methyl-4-piperidinyl)thio–4-methylisoleucine-cyclosporin

3-(N-methyl-4-piperidinyl)thio–4-methylisoleucine-cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–4-methylisoleucine-cyclosporin

3-(2-Hydroxyethyl)thio-8-(D)-serine-cyclosporin

3-(3-Hydroxypropyl)thio-8-(D)-serine-cyclosporin

3-(2-Aminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Methylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Ethylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Ethyl-N-methylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Diethylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Propylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Cyclopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Propyl-methylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Propyl-ethylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Methyl-isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Methylcyclopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Ethyl-isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Diisopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Propyl-isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Butylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-sec-Butylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Isobutylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-tert-Butylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Butyl-methylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Butyl-ethylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-n-Butyl-isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-sec-Butyl-methylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-sec-Butyl-ethylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-sec-Butyl-isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-tert-Butyl-methylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-tert-Butyl-ethylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-tert-Butyl-isopropylaminoethyl)thio-8-(D)-serine-cyclosporin

3-(2-Azetidinoethyl)thio-8-(D)-serine-cyclosporin

3-(2-pyrrolidinoethyl)thio-8-(D)-serine-cyclosporin

3-(2-piperidinoethyl)thio-8-(D)-serine-cyclosporin

3-(2-morpholinoethyl)thio-8-(D)-serine-cyclosporin

3-(2-piperazinoethyl)thio-8-(D)-serine-cyclosporin

3-(2-N-methylpiperazinoethyl)thio-8-(D)-serine-cyclosporin

3-(2-N-tert-butylpiperazinoethyl)thio-8-(D)-serine-cyclosporin

3-(3-azetidinyl)thio-8-(D)-serine-cyclosporin

3-(N-methyl-3-azetidinyl)thio-8-(D)-serine-cyclosporin

3-(N-methyl-3-azetidinyl)thio-8-(D)-serine-cyclosporin

3-(N-isopropyl-3-azetidinyl)thio–8-(D)-serine-cyclosporin

3-(3-pyrrolidinyl)thio-8-(D)-serine-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–8-(D)-serine-cyclosporin

3-(N-methyl-3-pyrrolidinyl)thio–8-(D)-serine-cyclosporin

3-(N-isopropyl-3-pyrrolidinyl)thio–8-(D)-serine-cyclosporin

3-(4-piperidinyl)thio–8-(D)-serine-cyclosporin

3-(N-methyl-4-piperidinyl)thio–8-(D)-serine-cyclosporin

3-(N-methyl-4-piperidinyl)thio–8-(D)-serine-cyclosporin

3-(N-isopropyl-4-piperidinyl)thio–8-(D)-serine-cyclosporin

3-(2-Hydroxyethoxy)-cyclosporin

3-(3-Hydroxypropoxy)-cyclosporin

3-(2-Chloroethoxy)-cyclosporin

3-(2-Bromoethoxy)-cyclosporin

3-(2-Hydroxyethoxy)-cyclosporin

3-(3-Chloropropoxy)-cyclosporin

3-(3-Bromopropoxy)-cyclosporin

3-(3-Hydroxypropoxy)-cyclosporin

3-(3-Chlorobutoxy)-cyclosporin

3-(3-Bromobutoxy)-cyclosporin

3-(2-Aminoethoxy)-cyclosporin

3-(2-Methylaminoethoxy)-cyclosporin

3-(2-Dimethylaminoethoxy)-cyclosporin

3-(2-Ethylaminoethoxy)-cyclosporin

3-(2-Ethyl-N-methylaminoethoxy)-cyclosporin

3-(2-Diethylaminoethoxy)-cyclosporin

3-(2-n-Propylaminoethoxy)-cyclosporin

3-(2-Isopropylaminoethoxy)-cyclosporin

3-(2-Cyclopropylaminoethoxy)-cyclosporin

3-(2-n-Propyl-methylaminoethoxy)-cyclosporin

3-(2-n-Propyl-ethylaminoethoxy)-cyclosporin

3-(2-Methyl-isopropylaminoethoxy)-cyclosporin

3-(2-Cyclopropylaminoethoxy)-cyclosporin

3-(2-Ethyl-isopropylaminoethoxy)-cyclosporin

3-(2-Diisopropylaminoethoxy)-cyclosporin

3-(2-n-Propyl-isopropylaminoethoxy)-cyclosporin

3-(2-n-Butylaminoethoxy)-cyclosporin

3-(2-sec-Butylaminoethoxy)-cyclosporin

3-(2-Isobutylaminoethoxy)-cyclosporin

3-(2-tert-Butylaminoethoxy)-cyclosporin

3-(2-n-Butyl-methylaminoethoxy)-cyclosporin

3-(2-n-Butyl-ethylaminoethoxy)-cyclosporin

3-(2-n-Butyl-isopropylaminoethoxy)-cyclosporin

3-(2-sec-Butyl-methylaminoethoxy)-cyclosporin

3-(2-sec-Butyl-ethylaminoethoxy)-cyclosporin

3-(2-sec-Butyl-isopropylaminoethoxy)-cyclosporin

3-(2-tert-Butyl-methylaminoethoxy)-cyclosporin

3-(2-tert-Butyl-ethylaminoethoxy)-cyclosporin

3-(2-tert-Butyl-isopropylaminoethoxy)-cyclosporin

3-(2-Azetidinoethoxy)-cyclosporin

3-(2-pyrrolidinoethoxy)-cyclosporin

3-(2-piperidinoethoxy)-cyclosporin

3-(2-morpholinoethoxy)-cyclosporin

3-(2-piperazinoethoxy)-cyclosporin

3-(2-N-methylpiperazinoethoxy)-cyclosporin

3-(2-N-methylpiperazinoethoxy)-cyclosporin

3-(2-N-isopropylpiperazinoethoxy)-cyclosporin

3-(3-azetidinyloxy)-cyclosporin

3-(N-methyl-3-azetidinyloxy)-cyclosporin

3-(N-isopropyl-3-azetidinyloxy)-cyclosporin

3-(N-tert-butyl-3-azetidinyloxy)–cyclosporin

3-(3-pyrrolidinyloxy)-cyclosporin

3-(N-methyl-3-pyrrolidinyloxy)–cyclosporin

3-(N-tert-butyl-3-pyrrolidinyloxy)–cyclosporin

3-(N-isopropyl-3-pyrrolidinyloxy)–cyclosporin

3-(4-piperidinyloxy)–cyclosporin

3-(N-methyl-4-piperidinyloxy)–cyclosporin

3-(N-isopropyl-4-piperidinyloxy)–cyclosporin

3-(N-tert-butyl-4-piperidinyloxy)–cyclosporin

3-(2-Hydroxyethoxy)-2-valine-cyclosporin

3-(3-Hydroxypropoxy)-2-valine-cyclosporin

3-(2-Chloroethoxy)- 2-valine-cyclosporin

3-(2-Bromoethoxy)- 2-valine-cyclosporin

3-(2-Hydroxyethoxy)- 2-valine-cyclosporin

3-(3-Chloropropoxy)- 2-valine-cyclosporin

3-(3-Bromopropoxy)- 2-valine-cyclosporin

3-(3-Hydroxypropoxy)- 2-valine-cyclosporin

3-(3-Chlorobutoxy)- 2-valine-cyclosporin

3-(3-Bromobutoxy)- 2-valine-cyclosporin3-(2-Aminoethoxy)-2-valine-cyclosporin

3-(2-Methylaminoethoxy)-2-valine-cyclosporin

3-(2-Dimethylaminoethoxy)-2-valine-cyclosporin

3-(2-Ethylaminoethoxy)-2-valine-cyclosporin

3-(2-Ethyl-N-methylaminoethoxy)-2-valine-cyclosporin

3-(2-Diethylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Propylaminoethoxy)-2-valine-cyclosporin

3-(2-Isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-Cyclopropylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Propyl-methylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Propyl-ethylaminoethoxy)-2-valine-cyclosporin

3-(2-Methyl-isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-Cyclopropylaminoethoxy)-2-valine-cyclosporin

3-(2-Ethyl-isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-Diisopropylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Propyl-isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Butylaminoethoxy)-2-valine-cyclosporin

3-(2-sec-Butylaminoethoxy)-2-valine-cyclosporin

3-(2-Isobutylaminoethoxy)-2-valine-cyclosporin

3-(2-tert-Butylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Butyl-methylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Butyl-ethylaminoethoxy)-2-valine-cyclosporin

3-(2-n-Butyl-isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-sec-Butyl-methylaminoethoxy)-2-valine-cyclosporin

3-(2-sec-Butyl-ethylaminoethoxy)-2-valine-cyclosporin

3-(2-sec-Butyl-isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-tert-Butyl-methylaminoethoxy)-2-valine-cyclosporin

3-(2-tert-Butyl-ethylaminoethoxy)-2-valine-cyclosporin

3-(2-tert-Butyl-isopropylaminoethoxy)-2-valine-cyclosporin

3-(2-Azetidinoethoxy)-2-valine-cyclosporin

3-(2-pyrrolidinoethoxy)-2-valine-cyclosporin

3-(2-piperidinoethoxy)-2-valine-cyclosporin

3-(2-morpholinoethoxy)-2-valine-cyclosporin

3-(2-piperazinoethoxy)-2-valine-cyclosporin

3-(2-N-methylpiperazinoethoxy)-2-valine-cyclosporin

3-(2-N-methylpiperazinoethoxy)-2-valine-cyclosporin

3-(2-N-isopropylpiperazinoethoxy)-2-valine-cyclosporin

3-(3-azetidinyloxy)-2-valine-cyclosporin

3-(N-methyl-3-azetidinyloxy)-2-valine-cyclosporin

3-(N-isopropyl-3-azetidinyloxy)-2-valine-cyclosporin

3-(N-tert-butyl-3-azetidinyloxy)–2-valine-cyclosporin

3-(3-pyrrolidinyloxy)-2-valine-cyclosporin

3-(N-methyl-3-pyrrolidinyloxy)–2-valine-cyclosporin

3-(N-tert-butyl-3-pyrrolidinyloxy)–2-valine-cyclosporin

3-(N-isopropyl-3-pyrrolidinyloxy)–2-valine-cyclosporin

3-(4-piperidinyloxy)–2-valine-cyclosporin

3-(N-methyl-4-piperidinyloxy)–2-valine-cyclosporin

3-(N-isopropyl-4-piperidinyloxy)–2-valine-cyclosporin

3-(N-tert-butyl-4-piperidinyloxy)–2-valine-cyclosporin

3-(2-Hydroxyethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Hydroxypropoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Chloroethoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Bromoethoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Hydroxyethoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Chloropropoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Bromopropoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Hydroxypropoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Chlorobutoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-Bromobutoxy)- 4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Aminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Methylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Dimethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Ethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Ethyl-N-methylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Diethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Cyclopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propyl-methylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propyl-ethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Methyl-isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Cyclopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Ethyl-isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Diisopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Propyl-isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Isobutylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butyl-methylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butyl-ethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-n-Butyl-isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butyl-methylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butyl-ethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-sec-Butyl-isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butyl-methylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butyl-ethylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-tert-Butyl-isopropylaminoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Azetidinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-pyrrolidinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-piperidinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-morpholinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-piperazinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-N-methylpiperazinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-N-methylpiperazinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-N-isopropylpiperazinoethoxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-azetidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-3-azetidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-isopropyl-3-azetidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-tert-butyl-3-azetidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(3-pyrrolidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-3-pyrrolidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-tert-butyl-3-pyrrolidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-isopropyl-3-pyrrolidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(4-piperidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-methyl-4-piperidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-isopropyl-4-piperidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(N-tert-butyl-4-piperidinyloxy)-4-(gamma-hydroxy-methylleucine)-cyclosporin

3-(2-Hydroxyethoxy)-2-norvaline-cyclosporin

3-(3-Hydroxypropoxy)-2-norvaline-cyclosporin

3-(2-Chloroethoxy)- 2-norvaline-cyclosporin

3-(2-Bromoethoxy)- 2-norvaline-cyclosporin

3-(2-Hydroxyethoxy)- 2-norvaline-cyclosporin

3-(3-Chloropropoxy)- 2-norvaline-cyclosporin

3-(3-Bromopropoxy)- 2-norvaline-cyclosporin

3-(3-Hydroxypropoxy)- 2-norvaline-cyclosporin

3-(3-Chlorobutoxy)- 2-norvaline-cyclosporin

3-(3-Bromobutoxy)- 2-norvaline-cyclosporin

3-(2-Aminoethoxy)-2-norvaline-cyclosporin

3-(2-Methylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Dimethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Ethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Ethyl-N-methylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Diethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Propylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Cyclopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Propyl-methylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Propyl-ethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Methyl-isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Cyclopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Ethyl-isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Diisopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Propyl-isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Butylaminoethoxy)-2-norvaline-cyclosporin

3-(2-sec-Butylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Isobutylaminoethoxy)-2-norvaline-cyclosporin

3-(2-tert-Butylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Butyl-methylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Butyl-ethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-n-Butyl-isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-sec-Butyl-methylaminoethoxy)-2-norvaline-cyclosporin

3-(2-sec-Butyl-ethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-sec-Butyl-isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-tert-Butyl-methylaminoethoxy)-2-norvaline-cyclosporin

3-(2-tert-Butyl-ethylaminoethoxy)-2-norvaline-cyclosporin

3-(2-tert-Butyl-isopropylaminoethoxy)-2-norvaline-cyclosporin

3-(2-Azetidinoethoxy)-2-norvaline-cyclosporin

3-(2-pyrrolidinoethoxy)-2-norvaline-cyclosporin

3-(2-piperidinoethoxy)-2-norvaline-cyclosporin

3-(2-morpholinoethoxy)-2-norvaline-cyclosporin

3-(2-piperazinoethoxy)-2-norvaline-cyclosporin

3-(2-N-methylpiperazinoethoxy)-2-norvaline-cyclosporin

3-(2-N-methylpiperazinoethoxy)-2-norvaline-cyclosporin

3-(2-N-isopropylpiperazinoethoxy)-2-norvaline-cyclosporin

3-(3-az tidinyloxy)-2-norvaline-cyclosporin

3-(N-methyl-3-azetidinyloxy)-2-norvaline-cyclosporin

3-(N-isopropyl-3-azetidinyloxy)-2-norvaline-cyclosporin

3-(N-tert-butyl-3-azetidinyloxy)–2-norvaline-cyclosporin

3-(3-pyrrolidinyloxy)-2-norvaline-cyclosporin

3-(N-methyl-3-pyrrolidinyloxy)–2-norvaline-cyclosporin

3-(N-tert-butyl-3-pyrrolidinyloxy)–2-norvaline-cyclosporin

3-(N-isopropyl-3-pyrrolidinyloxy)–2-norvaline-cyclosporin

3-(4-piperidinyloxy)–2-norvaline-cyclosporin

3-(N-methyl-4-piperidinyloxy)–2-norvaline-cyclosporin

3-(N-isopropyl-4-piperidinyloxy)–2-norvaline-cyclosporin

3-(N-tert-butyl-4-piperidinyloxy)–2-norvaline-cyclosporin

3-(2-Hydroxyethoxy)-4-methylvaline-cyclosporin

3-(3-Hydroxypropoxy)-4-methylvaline-cyclosporin

3-(2-Chloroethoxy)- 4-methylvaline-cyclosporin

3-(2-Bromoethoxy)- 4-methylvaline-cyclosporin

3-(2-Hydroxyethoxy)- 4-methylvaline-cyclosporin

3-(3-Chloropropoxy)- 4-methylvaline-cyclosporin

3-(3-Bromopropoxy)- 4-methylvaline-cyclosporin

3-(3-Hydroxypropoxy)- 4-methylvaline-cyclosporin

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3-(2-Cyclopropylaminoethoxy)-4-methylvaline-cyclosporin

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3-(2-n-Propyl-ethylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-Methyl-isopropylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-Cyclopropylaminoethoxy)-4-methylvaline-cyclosporin

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3-(2-Diisopropylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-n-Propyl-isopropylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-n-Butylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-sec-Butylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-Isobutylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-tert-Butylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-n-Butyl-methylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-n-Butyl-ethylaminoethoxy)-4-methylvaline-cyclosporin

3-(2-n-Butyl-isopropylaminoethoxy)-4-methylvaline-cyclosporin

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3-(2-N-methylpiperazinoethoxy)-4-methylvaline-cyclosporin

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3-(N-methyl-3-azetidinyloxy)-4-methylvaline-cyclosporin

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3-(4-piperidinyloxy)–4-methylvaline-cyclosporin

3-(N-methyl-4-piperidinyloxy)–4-methylvaline-cyclosporin

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3-(2-Hydroxyethoxy)-4-methylisoleucine-cyclosporin

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3-(2-Bromoethoxy)- 4-methylisoleucine-cyclosporin

3-(2-Hydroxyethoxy)- 4-methylisoleucine-cyclosporin

3-(3-Chloropropoxy)- 4-methylisoleucine-cyclosporin

3-(3-Bromopropoxy)- 4-methylisoleucine-cyclosporin

3-(3-Hydroxypropoxy)- 4-methylisoleucine-cyclosporin

3-(3-Chlorobutoxy)- 4-methylisoleucine-cyclosporin

3-(3-Bromobutoxy)- 4-methylisoleucine-cyclosporin

3-(2-Aminoethoxy)-4-methylisoleucine-cyclosporin

3-(2-Methylaminoethoxy)-4-methylisoleucine-cyclosporin

3-(2-Dimethylaminoethoxy)-4-methylisoleucine-cyclosporin

3-(2-Ethylaminoethoxy)-4-methylisoleucine-cyclosporin

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3-(2-sec-Butyl-methylaminoethoxy)-4-methylisoleucine-cyclosporin

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3-(2-N-methylpiperazinoethoxy)-4-methylisoleucine-cyclosporin

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3-(3-azetidinyloxy)-4-methylisoleucine-cyclosporin

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3-(N-tert-butyl-3-azetidinyloxy)—4-methylisoleucine-cyclosporin

3-(3-pyrrolidinyloxy)-4-methylisoleucine-cyclosporin

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3-(2-Hydroxyethoxy)- 8-(D)-serine-cyclosporin

3-(3-Chloropropoxy)- 8-(D)-serine-cyclosporin

3-(3-Bromopropoxy)- 8-(D)-serine-cyclosporin

3-(3-Hydroxypropoxy)- 8-(D)-serine-cyclosporin

3-(3-Chlorobutoxy)- 8-(D)-serine-cyclosporin

3-(3-Bromobutoxy)- 8-(D)-serine-cyclosporin

3-(2-Aminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Methylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Dimethylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Ethylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Ethyl-N-methylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Diethylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-n-Propylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Isopropylaminoethoxy)-8-(D)-serine-cyclosporin

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3-(2-Cyclopropylaminoethoxy)-8-(D)-serine-cyclosporin

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3-(2-n-Propyl-isopropylaminoethoxy)-8-(D)-serine-cyclosporin

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3-(2-sec-Butylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-Isobutylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-tert-Butylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-n-Butyl-methylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-n-Butyl-ethylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-n-Butyl-isopropylaminoethoxy)-8-(D)-serine-cyclosporin

3-(2-sec-Butyl-methylaminoethoxy)-8-(D)-serine-cyclosporin

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3-(2-piperidinoethoxy)-8-(D)-serine-cyclosporin

3-(2-morpholinoethoxy)-8-(D)-serine-cyclosporin

3-(2-piperazinoethoxy)-8-(D)-serine-cyclosporin

3-(2-N-methylpiperazinoethoxy)-8-(D)-serine-cyclosporin

3-(2-N-methylpiperazinoethoxy)-8-(D)-serine-cyclosporin

3-(2-N-isopropylpiperazinoethoxy)-8-(D)-serine-cyclosporin

3-(3-azetidinyloxy)-8-(D)-serine-cyclosporin

3-(N-methyl-3-azetidinyloxy)-8-(D)-serine-cyclosporin

3-(N-isopropyl-3-azetidinyloxy)-8-(D)-serine-cyclosporin

3-(N-tert-butyl-3-azetidinyloxy)–8-(D)-serine-cyclosporin

3-(3-pyrrolidinyloxy)-8-(D)-serine-cyclosporin

3-(N-methyl-3-pyrrolidinyloxy)–8-(D)-serine-cyclosporin

3-(N-tert-butyl-3-pyrrolidinyloxy)–8-(D)-serine-cyclosporin

3-(N-isopropyl-3-pyrrolidinyloxy)–8-(D)-serine-cyclosporin

3-(4-piperidinyloxy)–8-(D)-serine-cyclosporin

3-(N-methyl-4-piperidinyloxy)–8-(D)-serine-cyclosporin

3-(N-isopropyl-4-piperidinyloxy)–8-(D)-serine-cyclosporin

3-(N-tert-butyl-4-piperidinyloxy)–8-(D)-serine-cyclosporin

36. Test for cyclophilin binding:

To measure the affinity and inhibition of test compounds for cyclophilin, the test described by H. Fliri in "Antibiotics and Antiviral compounds", 1993, Verlag Chemie, K.Krohn, H.A. Kirst, and H. Maag, eds., p 229-240 was used. The activity of the test compounds shown in the table is expressed as relative IC50, i.e. IC50 (cyclosporin A)/IC50 (test compound):

Product of example	Relative IC50 (ng/ml)
1	0.2
2	0.2
3	0.2
4	0.2
5	0.2
6	0.2
7	0.2
8	0.4
9	1
12	1.5
13	1.5
14	2
15	2

37 Test for inhibition of cyclophilin :

The test described by G. Fischer et al., Biomed. Biochim. Acta, Vol. 43, 1101 - 1111 (1984) was used. Specifically, 5 µL of a 1µM solution of recombinant human cyclophilin 18 was dissolved, at 10,0 ± 0.3°C in 1250 µL HEPES buffer ; α-chymotrypsin was added to give a final concentration of 30 µM. Test compounds were dissolved in DMSO as 10 µM solutions and added to the enzyme solution to give final concentrations of 0.1, 0.5, 1.0, 5.0, 10.0, 50.0, 100.0, 500.0, and 1000 nM concentrations. After 5 minutes preincubation, Succ-Ala-Phe-Pro-Phe-4-nitroanilide was added to give a final concentration of 50 µM. The hydrolysis of the substrate was measured

spectrophotometrically at 390 - 450 nM. The following IC^{50} values were obtained :

Product of Example	Name	IC50 [nM]
	Cyclosporin A	12.43 ± 0.40
14	3-Methoxy-cyclosporin	11.57 ± 1.59
15	3-Ethoxy-cyclosporin	11.13 ± 1.03
16	3-Isopropoxy-cyclosporin	20.39 ± 1.26
17	3-tert-Butoxy-cyclosporin	18.94 ± 1.03
18	3-Allyloxy-cyclosporin	10.15 ± 2.21

38. Inhibition of HIV replication

The inhibitory effect of test compounds on the HIV-induced cytopathic effect on the MT4 T cell line as described by R. Pauwels in J. Virol. Methods, 1988, Vol. 20, pp 309-321 was used. The activity of test compounds is shown in the table:

Product of example	IC50 (ng/ml)
1	450
2	1000
3	1000
4	1000
5	1000
6	1000
7	1000
8	500
9	30
12	150
13	150
14	100

15 80

39. Activity against Toxoplasma gondii:

Using microtiter plates, T. gondii tachyzoites, strain RH were co-incubated with fibroblasts (MRC5, Bio-Merieux) for 72 hrs in the presence and absence of test compounds. T. gondii was quantified using an ELISA. The activities of the test compounds are as follows:

Product of example	Activity against T. gondii (IC50, µg/ml)
9	0.1
13	1
14	0.6
15	0.6

40 Antiinflammatory activity

The antiinflammatory activity of test compounds was determined by the adjuvant arthritis test described by Pearson, "Arthr. Rheum", 1959, Vol. 2., 440. Test compounds were administered orally as solutions in olive oil and tween 80. Their activity is expressed as ED50 in mg/kg, i.e. the dose effective in reducing the joint swelling by 50%, and is as shown below.

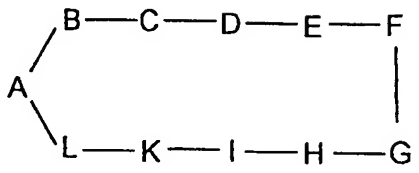
Product of example	ED50 (mg/kg)
1	25
2	25
3	25
4	25
5	25
6	25
7	25
8	25
9	15

12	15
13	15
14	10
15	15

Claims:

What we claim is

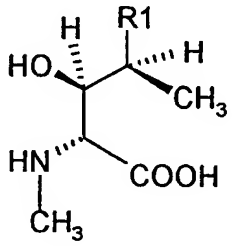
1. A compound of formula I



Formula I

and its pharmaceutically acceptable salts wherein the letters A to L represent residues of the following amino acids:

A (L)-alpha-N-methylamino-beta-hydroxy acid of the formula II,

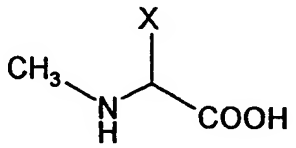


Formula II

wherein R1 is n-butyl or butenyl-1

B alpha-amino-butyric acid, alpha-amino-valerianic acid (norvaline), threonine, or valine,

C substituted sarcosine of the formula III



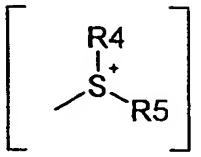
Formula III

in which X is

$S-(O)_n-R2$, in which n has the value zero, one or two and R2 is hydrogen, unsubstituted or substituted, unbranched or branched, acyclic, monocyclic or polycyclic, saturated or unsaturated lower alkyl, substituted or unsubstituted aryl or heteroaryl, or

X is O-R3, in which R3 is hydrogen, unsubstituted or substituted, unbranched or branched, saturated or unsaturated, acyclic, monocyclic or polycyclic lower alkyl, or acyl, or

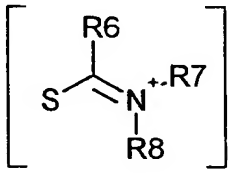
X is a sulfonium group of the formula IV,



Formula IV

in which R4 and R5 are independently selected from lower alkyl, aryl, or heteroaryl and Y^- is an anion, or

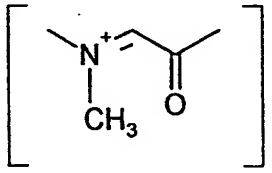
X is a group of the formula V,



Formula V

in which R6 and R7 are independently selected from lower alkyl or aryl or form together a ring and R8 is hydrogen or substituted or unsubstituted lower alkyl and Y^- is an anion, or

C is a residue of the formula VI and Y^- is an anion



Formula VI

D is N-methyl-leucine, gamma-hydroxy-N-methyl-leucine, N-methyl-valine, or N-methyl-isoleucine,

E is valine,

F is N-methyl-leucine,

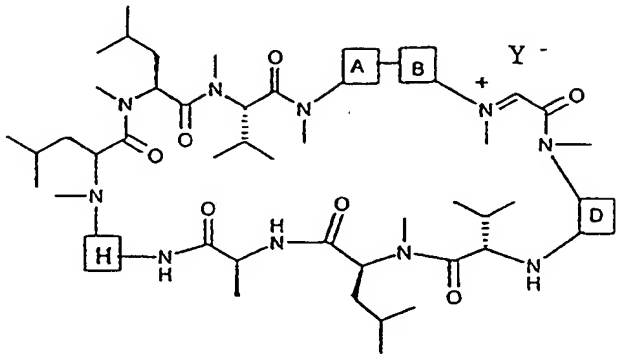
G is alanine,

H is glycine, (D)-alanine, (D)-serine, O-hydroxyethyl-(D)-serine,

I,K are N-methyl-leucine, and

L is N-methyl-valine.

2. A compound of formula VII, in which A, B, D, and H have the above definitions and Y⁻ is an anion



Formula VII

3. A compound of formula I in which C is a substituted sarcosine of the formula III and in which X is SH.
4. A process for the synthesis of compounds of the formula I, in which C is sarcosine substituted by S-R2, characterized by forming from cyclosporins in which C is sarcosine respective polyanions and reacting these polyanions with sulfur electrophiles.
5. A process for the synthesis of compounds of the formula I, in which C is sarcosine substituted by S-R2 and in which R2 is hydrogen, characterized by treating compounds of formula 1, in which C is sarcosine substituted by X and where X is a residue of the formula IV or V with a thio acid to give compounds of formula 1 in which C is sarcosine substituted by S-R2 and in which R2 is acyl, with ammonia, hydrazine, hydroxylamine or organic derivatives thereof.
6. A process for the synthesis of compounds of the formula I, in which C is sarcosine substituted by S-R2 and in which R2 is substituted or unsubstituted, branched or unbranched, saturated or unsaturated, acyclic, monocyclic, or polycyclic lower alkyl by treating compounds of formula 1 in which C is sarcosine substituted by SH with alkylating agents.

7. A process for the synthesis of compounds of the formula I, in which C is sarcosine substituted by SO-R2 and by SO2-R2, characterized by treating compounds of formula I in which C is sarcosine substituted by S-R2 with an appropriate oxidant in an inert solvent.
8. A process for the synthesis of compounds of the formula I, in which C is sarcosine substituted by O-R3, characterized by exchanging the substituent S-R2 in compounds of formula I in which C is sarcosine substituted by S-R2.
9. A process for the synthesis of compounds of the formula I, in which C is sarcosine substituted by O-R3, characterized by exchanging the substituent O-R3' in compounds of formula I in which C is sarcosine substituted by O-R3'.
10. Use of compounds of formula 1 and its pharmaceutically acceptable salts as pharmaceuticals and for the manufacture of pharmaceutical compositions.
11. Use of compounds of formula 1 and its pharmaceutically acceptable salts as inhibitors of cyclophilins.
12. Use of compounds of formula 1 and its pharmaceutically acceptable salts for the treatment of infectious diseases caused by bacterial, fungal, viral pathogens as well as by protozoan parasites and helminthes.
13. Use of compounds of formula 1 and its pharmaceutically acceptable salts for the treatment of chronic inflammatory and autoimmune diseases.
14. Use of compounds of formula 1 and its pharmaceutically acceptable salts for the treatment of pathologic conditions caused by trauma and reperfusion injury.
15. Use of compounds of formula 1 and its pharmaceutically acceptable salts to induce tissue regenerative processes.

INTERNATIONAL SEARCH REPORT

International A, :ation No
PCT/EP 99/04012

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K7/64 A61K38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	FR 2 757 520 A (RHONE POULENC RORER SA) 26 June 1998 (1998-06-26) the whole document	1,4,6
P,X	FR 2 757 521 A (RHONE POULENC RORER SA) 26 June 1998 (1998-06-26) the whole document	1,4,6
P,X	FR 2 757 522 A (RHONE POULENC RORER SA) 26 June 1998 (1998-06-26) the whole document	1,4,6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1999	22/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 194 972 A (SANDOZ AG ;SANDOZ AG (DE); SANDOZ AG (AT)) 17 September 1986 (1986-09-17) cited in the application abstract page 26 page 43-44 page 7 -page 10 page 21 -page 22 ---	1,2,4,6, 7,10-15
X	SEEBACH D ET AL: "MODIFICATION OF CYCLOSPORIN A (CS): GENERATION OF AN ENOLATE AT THESARCOSINE RESIDUE AND REACTIONS WITH ELECTROPHILES" HELVETICA CHIMICA ACTA, vol. 76, no. 4, 1 January 1993 (1993-01-01), pages 1564-1590, XP002022424 ISSN: 0018-019X Scheme 2 table 1 ---	1,2,4,6
X	WO 97 04005 A (CHEM AG C ;LUECHINGER JEAN M (CH)) 6 February 1997 (1997-02-06) page 4; claims -----	1,2,4,6, 7,10-15

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatio pplication No.
PCT/EP 99/04012

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 10-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/04012

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2757520 A	26-06-1998	AU 5669198 A	17-07-1998
		WO 9828328 A	02-07-1998
		US 5948755 A	07-09-1999
FR 2757521 A	26-06-1998	AU 5669398 A	17-07-1998
		WO 9828330 A	02-07-1998
FR 2757522 A	26-06-1998	AU 5669298 A	17-07-1998
		EP 0948527 A	13-10-1999
		WO 9828329 A	02-07-1998
EP 0194972 A	17-09-1986	AT 78832 T	15-08-1992
		AU 3817689 A	02-11-1989
		AU 588860 B	28-09-1989
		AU 5448586 A	18-09-1986
		DE 3686183 A	03-09-1992
		DK 109486 A	12-09-1986
		ES 552855 A	16-01-1989
		ES 557619 A	16-07-1988
		FI 860993 A	12-09-1986
		GR 860646 A	11-07-1986
		JP 2027143 C	26-02-1996
		JP 7059594 B	28-06-1995
		JP 61212599 A	20-09-1986
		NZ 215414 A	28-08-1990
		PH 22439 A	12-09-1988
		PT 82164 A,B	01-04-1986
		US 4771122 A	13-09-1988
		US 4703033 A	27-10-1987
WO 9704005 A	06-02-1997	AU 6700196 A	18-02-1997
		BR 9609795 A	16-03-1999
		CA 2226880 A	06-02-1997
		CN 1192750 A	09-09-1998
		CZ 9800051 A	15-04-1998
		EP 0842191 A	20-05-1998
		HU 9900405 A	28-06-1999
		NO 980195 A	15-01-1998
		PL 324531 A	08-06-1998
		US 5948884 A	07-09-1999